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Approach to desensitization in aspirin-exacerbated respiratory disease

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- Describe a systematic approach to evaluating and treating patients with suspected aspirin exacerbated respiratory disease

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Clinical Vignette

A 44-year-old woman presented to the allergy clinic for evaluation of chronic rhinosinusitis and persistent asthma. Her respiratory symptoms developed 8 years previously as isolated nasal

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Table 1
Clinical factors to strengthen or weaken the diagnosis of AERD in patients with chronic sinusitis and asthma

Higher likelihood of AERD	Lower likelihood of AERD
Pansinusitis by imaging	Minimal or moderate unilateral radiographic sinus disease[a]
Severe persistent asthma	Mild to moderate asthma
Complete anosmia	No anosmia
Refractory to sinus surgery/ polypectomy	Durable response to sinus surgery/ polypectomy
Sinusitis incompletely responsive to antibiotics and corticosteroids	Sinusitis responds to antibiotics and corticosteroids
Age of onset in the 30s	Onset in childhood or adolescence
Respiratory reaction with any NSAID or aspirin	Tolerates any NSAID or aspirin[b]

Abbreviations: AERD, aspirin-exacerbated respiratory disease; NSAID, nonsteroidal anti-inflammatory drug.
[a]Extremely low likelihood of AERD.
[b]Excludes possibility of AERD.

congestion and rhinorrhea. She subsequently developed anosmia and pansinusitis with nasal polyposis. Three years later, she developed severe, persistent asthma that was well controlled with inhaled corticosteroid and long-acting β agonist combination therapy and montelukast.

Her sinus disease had been refractory to antibiotics and topical nasal fluticasone (2 sprays daily in each nostril), and she had experienced only temporary relief with oral prednisone. In total, she had undergone 3 polypectomies, each time with recurrence of symptoms within 1 to 2 years. She had no history of atopy or respiratory disease. She was a lifetime nonsmoker but did have considerable secondhand tobacco smoke exposure in childhood. Her examination showed nasal obstruction and bilateral polyps. Lungs were clear without wheezing. Cross-sectional sinus imaging visualized near total pan-sinus opacification bilaterally.

The patient had no history of aspirin (acetylsalicylic acid [ASA]) or nonsteroidal anti-inflammatory drug (NSAID) reaction but did not recall taking any such medication in recent years. She had tolerated acetaminophen and had no suspected food allergies, but she had noticed increased nasal symptoms after consumption of red wine.

Introduction

Reports of respiratory symptoms after ASA ingestion occurred in the early 20th century, and the syndrome of ASA-exacerbated respiratory disease (AERD), asthma, nasal polyps, and ASA-induced respiratory symptoms was well characterized by Samter and Beers[1] in 1968. In 1980, Stevenson et al[2] published the first case of therapeutic ASA desensitization for the treatment of AERD. Despite an increased understanding of AERD, it continues to present unique challenges in disease recognition and treatment.

Diagnosis

Despite the availability of effective treatment, AERD remains under-recognized. Unfortunately, no simple screening test exists for AERD. The only definitive means of diagnosis is to elicit a positive reaction during a provocative challenge.[3] Approximately 5% to 9% of patients with asthma and one third of those with asthma and nasal polyps show evidence of AERD at provocative challenges.[4,5] Most patients with AERD provide clues, supplied by history and physical examination, to guide the clinician (Table 1).

Most patients report an onset of symptoms at 20 to 40 years of age, but rare cases have been reported in adults older than 70 years and children as young as 5 years.[5–7] A common story is that of initially developing symptoms of an acute upper respiratory tract infection that evolve to chronic nasal obstruction, rhinorrhea, and anosmia with eventual progression to severe chronic rhinosinusitis.[5,8] Development of asthma typically lags 1 to 2 years behind nasal and sinus symptoms.[5,8] Although sinus disease is universal in AERD, a minority may not have asthma or even bronchial hyper-reactivity as defined by a methacholine challenge.

In patients with AERD, asthma and sinus disease are typically severe. Most patients complain of anosmia and virtually all present with radiographic sinus opacification and nasal polyposis.[5] The severity of sinusitis by cross-sectional imaging has been shown to correlate with the likelihood of a positive ASA challenge result.[9] Thus, it is common for patients with AERD to have undergone numerous sinus or polyp surgeries, the need for which appears to be due to the accelerated rate of polyp growth in patients with AERD.[10] Asthma also is typically severe in patients with AERD, with 4 of 5 of requiring an inhaled corticosteroid.[8] Peripheral eosinophilia also is frequently present and may serve as a diagnostic clue.[2,11]

A history of respiratory reaction with antagonism of cyclooxygenase (COX) 1 is helpful, but not always present. Any medication with significant COX-1 blocking activity has the potential to induce symptoms in AERD. Most patients who have unknowingly taken full therapeutic doses of NSAIDs will describe associated severe asthma episodes frequently requiring emergency medical intervention. However, as many as 15% of patients with AERD are unaware of their underlying NSAID or ASA sensitivity until the time of oral challenge; therefore, the lack of a positive reaction history does not exclude the diagnosis of AERD.[8] In a study of patients with sinusitis, asthma, and nasal polyps but no known prior exposure to NSAIDs, 42% had a positive provocative challenge reaction compared with 80% to 89% in the same population with a positive NSAID history.[12] The remaining 11% to 20% of patients, with typical features suggestive of AERD but a negative challenge result with ASA, did not experience respiratory disease improvement with ASA therapy.[12]

Selective COX-2 inhibitors are nearly always well tolerated. Foods containing salicylate also are well tolerated, and patients should not be instructed to avoid these unless the history specifically suggests otherwise.

Pathophysiology

Aspirin-exacerbated respiratory disease is a clinical manifestation of underlying respiratory mucosal inflammation that is constant but made acutely worse by COX-1 inhibition.[13] The etiology of underlying inflammation is not fully understood, but there is evidence for overproduction of cysteinyl leukotrienes (LTs).[3] AERD is not mediated by IgE.[13]

The pathophysiology of AERD is highly complex. A review of the pathophysiology was recently published by Laidlaw and Boyce,[14] which is summarized in Figure 1. The most notable abnormality in AERD centers on the tenuous balance of COX-1 activity and prostaglandin E_2 (PGE_2) inhibition of 5-lipxygenase. Under normal physiologic conditions, sufficient COX-1 activity leads to adequate synthesis of PGE_2, which has immunoregulatory activity. In particular, PGE_2 inhibits 5-lipxygenase–mediated synthesis of LTs, including LTC_4, LTD_4, and LTE_4.[14] When ASA or NSAID antagonizes COX-1 activity, PGE_2 synthesis decreases, thereby “releasing the brake” on 5-lipxygenase–mediated LT production. In tolerant individuals, sufficient residual COX-2 activity is present, preserves adequate PGE_2 synthesis, and keeps the net effect of COX-1 inhibition and consequent PGE_2 depletion within normal physiologic parameters.[14] The net result in patients with AERD after ASA ingestion is a marked increase in LT production and associated acute worsening in respiratory symptoms. These increased LTs can be detected in the urine in the form of LTE_4, which has been found to be elevated at baseline in many patients with AERD and to increase further after ASA or NSAID exposure.[15]

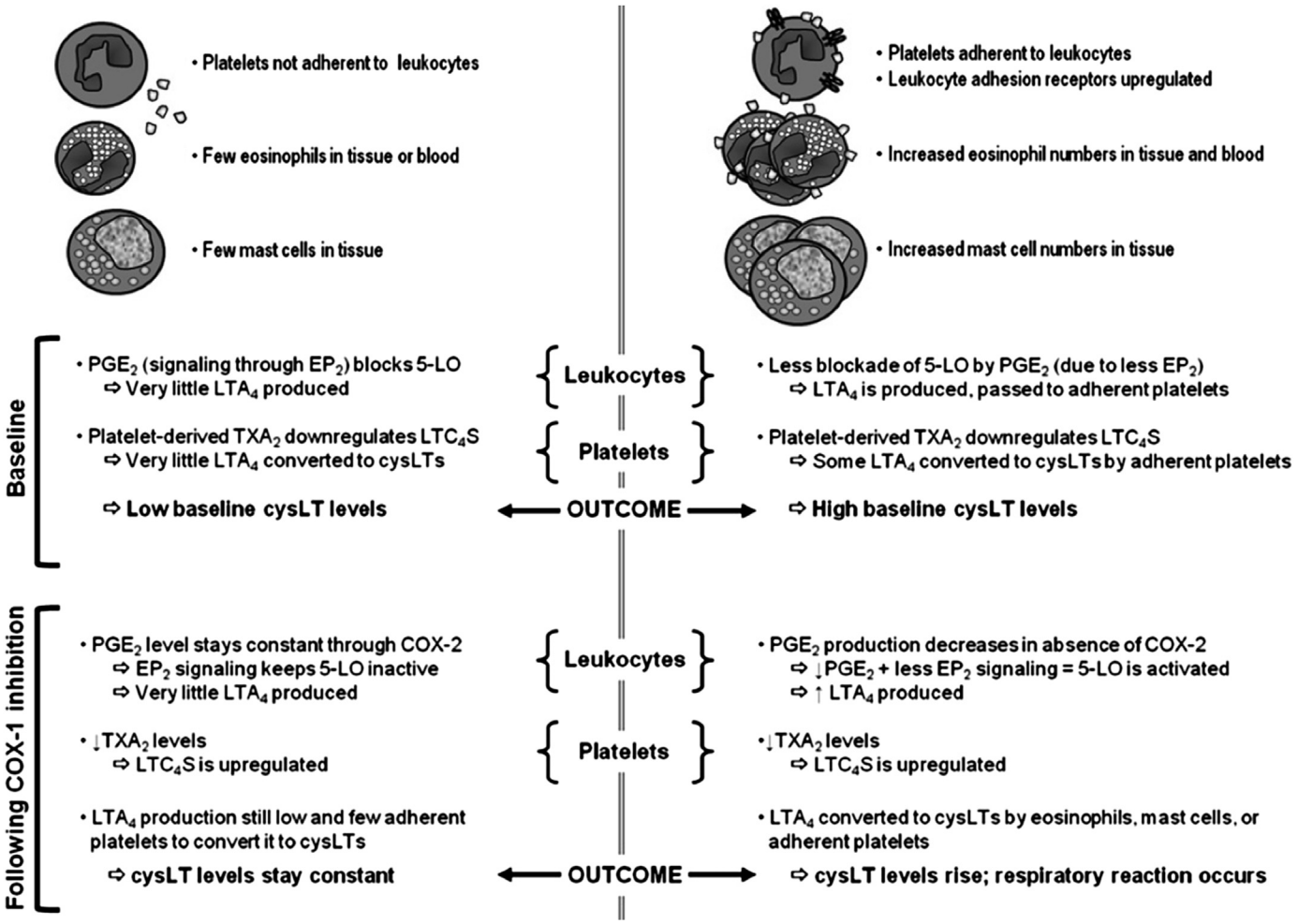

Figure 1. Pathophysiology of aspirin-exacerbated respiratory disease. *(Left)* The physiologic state of aspirin-tolerant patients is displayed at baseline and after cyclooxygenase-1 (COX-1) inhibition. *(Right)* The aberrances at baseline and after COX-1 inhibition in patients with aspirin-exacerbated respiratory disease are shown. 5-LO, 5-lipxygenase; COX-2, cyclooxygenase-2; cysLTs, cysteinyl leukotrienes; EP_2, E prostanoid 2 receptor; LTA_4, leukotriene A_4; LTC_4S, leukotriene C_4S; PGE_2, prostaglandin E_2; TXA_2, thromboxane A_2. Reproduced with permission from Figure 1 in Laidlaw and Boyce.[14]

Challenge and Desensitization

Safety

Provocative ASA challenge can generally be performed safely in an outpatient clinic by physicians trained in the treatment of asthma and allergic disease. Self-reported provocative dose and reaction severity for asthma attacks after ASA or NSAID exposure are not predictive of the severity of reaction observed during a provocative challenge.[16] Risk factors that have been shown to correlate with moderate to severe bronchial reaction during an ASA challenge include impaired baseline forced expiration in 1 second (FEV_1), prior emergency room visits for asthma, age 30 to 40 years, and a duration of AERD symptoms shorter than 10 years.[17] A provocative challenge should not be performed if the baseline FEV_1 is less than 50% predicted or usually less than 1 L.[18]

Treatment with LT modifiers, including montelukast, zafirlukast, and zileuton, before an ASA challenge decreases the likelihood of severe lower respiratory reactions without significantly masking upper respiratory symptoms.[17] In particular, the administration of montelukast for at least 1 week before an oral ASA challenge has consistently been shown to decrease the risk of bronchospastic reactions and preserve naso-ocular symptoms, thus increasing safety without increasing the frequency of false-negative challenge results.[17,19] Medications that should be withheld before a provocative challenge include inhaled short-acting β agonists, inhaled anticholinergics, and oral antihistamines.[20] The duration that each of these should be withheld is based on each medication's respective half-life.

Dosing

Unlike graded challenges in IgE-mediated drug allergy, the starting dose for a provocative ASA challenge in AERD is much higher, typically 20 to 40 mg.[17] Most bronchial and naso-ocular reactions occur at a dose range of 45 to 100 mg and within 30 to 60 minutes of dosing.[17] The typical interval between doses during a challenge is 90 to 180 minutes. However, reactions can occur as many as 3 hours after dosing, especially if lower doses are given.[20] A typical sequence of oral ASA dosing would be 30, 45, 60, 100, 150, and 325 mg.[21] A modified protocol uses nasal ketorolac before oral ASA, which is safe, effective, and less time consuming.[21] In this modified protocol, ketorolac tromethamine is diluted into normal saline to a concentration of 12.6 mg/mL and administered through a nasal spray device at 100 μL per actuation (1.26 mg/spray) according to the dosing protocol outlined in Table 2.[21] The usage of a double-blinded challenge would be ideal to ensure accuracy and avoid overdiagnosis but is not commonly used in practice because of the associated increased time requirements. After a final desensitization dose of 325 mg, patients with suspected AERD are discharged on 650 mg of ASA twice daily with a plan to down titrate

Table 2
Outpatient aspirin oral provocative challenge and desensitization for aspirin-exacerbated respiratory disease as currently performed at the Scripps Clinic

Time (min)	Medications	Dosage (mg)	Route
Day 1			
0	nasal ketorolac	1.26	1 spray 1 nostril
30	nasal ketorolac	2.53	1 spray each nostril
60	nasal ketorolac	5.05	2 sprays each nostril
90	nasal ketorolac	7.58	3 sprays each nostril
180	aspirin	60	oral
270	aspirin	60	oral
Day 2			
0	aspirin	150	oral
180	aspirin	325	oral
360	patient discharged		

by 325 mg each month to a lowest effective dose or a minimum dose of 325 mg twice daily.[22,23] Doses lower than 325 mg/d, such as those that might be administered to maintain ASA desensitization in cardiac conditions, have generally not been efficacious in the treatment of AERD.

Once desensitized, a patient will maintain the desensitization status for 48 to 72 hours between doses of ASA. Therefore, if a patient misses 1 day of ASA, then it can be resumed at the previous dose. However, if at least 48 hours has lapsed without ASA dosing, then the risk of reaction with any COX-1 inhibition begins to re-emerge.

Long-Term Treatment

Long-term ASA therapy is effective in as many as 87% of patients.[24] At 6 months of treatment, patients exhibit decreased acute sinusitis episodes, improved symptom scores, improved olfactory scores, and decreased systemic corticosteroid use.[24] These benefits persist for longer than 10 years.[25] Owing to the phenomenon of cross-desensitization, ASA-desensitized patients may take any type of other NSAID without the risk of a respiratory reaction. Other medical management of AERD is similar to that of chronic sinus disease, nasal polyp disease, and asthma in patients with non-AERD, but with an emphasis on the role for LT modifiers. As with any chronic polyp disease, aggressive topical nasal corticosteroids are integral to treatment and generally should be continued in conjunction with long-term ASA therapy. However, even with a combination of long-term ASA therapy and aggressive medical management, many patients might eventually require repeat polypectomy.

The physician and patient should discuss the risks of long-term ASA therapy before deciding on a regimen. These include increased risks of bleeding, gastrointestinal upset or ulcer, and missing at least 2 doses, potentially resulting in the loss of desensitization status. In addition, patients requiring elective surgery, such as nasal polypectomy, may need to withhold ASA before surgery to mitigate bleeding. In such cases, if ASA is withheld for longer than 48 to 72 hours, then repeat desensitization is indicated before resuming ASA.

Case Revisited

The patient was suspected to have AERD based on her history of severe sinusitis, refractory polyp disease, and adult-onset, severe, persistent asthma. Although she had no history of NSAID or ASA exposure, the likelihood of her having a positive challenge reaction was estimated at 42%.[12]

She returned for an ASA provocative challenge and desensitization in the outpatient clinic. Her baseline FEV_1 was 86% predicted. After premedication with montelukast, she received sequentially increasing doses of intranasal ketorolac. After her third dose, she experienced naso-ocular and chest reactions characterized by tearing, nasal congestion, and mild chest tightness and wheeze. She had a concordant 11% decrease in her FEV_1 that reversed with a bronchodilator and her naso-ocular symptoms resolved with oral cetirizine and topical nasal decongestant. She subsequently received escalating doses of oral ASA according to the 2-day standard protocol to a maximum dose of 325 mg, with no further reaction.

After the desensitization protocol, she was discharged on 650 mg of oral ASA twice per day with a plan to decrease by 325 mg each month to a minimum dose of 325 mg twice daily. She found her minimal effective dose to be 650 mg each morning and 325 mg each evening, which she has continued for the past year, with improved sinus and chest symptoms.

Conclusion

Aspirin-exacerbated respiratory disease is characterized by the triad of nasal polyposis, bronchial asthma, and ASA or NSAID sensitivity. Common characteristics of patients with AERD include severe sinusitis, persistent asthma, anosmia, and refractory nasal polyp disease. The pathophysiology of AERD involves aggressive, underlying respiratory mucosal inflammation that is acutely worsened by COX-1 inhibition. Although effective treatment exists, AERD remains under-recognized. An observed reaction during a provocative challenge remains the only definitive means of diagnosis. Clinicians should keep in mind that not all patients with AERD have a definitive personal history of ASA or NSAID reactivity.

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